disease prevention news

August 31, 1998 Vol. 58, No. 18

Diabetic Nephropathy—Can It Be Prevented?

Today, over 6% of the population has diabetes, and non—insulin-dependent diabetes mellitus accounts for 95% of all cases. Thirty years ago less than 2% of the population had diabetes mellitus. In the United States the number of patients progressing to end stage renal disease is increasing at an alarming rate. Health professionals must ensure that all patients have access to early diagnosis and appropriate treatment for diabetic nephropathy.

Three causes are cited for the dramatic rise in non—insulin-dependent diabetes mellitis (NIDDM):

- The population is aging.
- A greater percentage of the population is obese.
- The rate of growth of minority populations with a high genetic risk of NIDDM exceeds the growth rate of the United State population as a whole.

Populations at high risk include African Americans, Asian Americans, and Mexican Americans. Mexican Americans are the most rapidly growing minority population in the United States.

While there has been a 3-fold increase in the prevalence of diabetes in the last 30 years, the number of diabetics on dialysis has increased 5-fold in the decade of 1982-1992 alone. The frequency of diabetes among individuals with end-stage renal disease (ESRD) was 13% in 1982, 26% in 1992, and is approximately 35% today.[1] In NIDDM the incidence of ESRD varies considerably among ethnic groups. It is estimated that 5% of Caucasians, 10% of Asian Americans, 20% of Black Americans and Mexican Americans, and up to 50% of Native Americans eventually will require dialysis.[2] The yearly medical cost per patient on dialysis is $47,000, with $38,400 paid through Medicare.

A genetic predisposition to nephropathy and a prolonged history of poor metabolic control both contribute to the development of ESRD in individual patients. Abnormalities in the Na^+-Li^+ counter-transport system, angiotensin-converting enzyme (ACE), gene polymorphisms, and insulin resistance are genetic factors that may increase the risk of ESRD in some families. Metabolic factors—including poor glycemic control, hypertension, and duration of diabetes—are all linked to the development and progression of nephropathy. Onset of NIDDM at an early age, a higher incidence of poor glycemic control and hypertension, and genetic susceptibility all contribute to the higher prevalence of nephropathy seen in minorities, including Mexican Americans in South Texas.

Development of Diabetic Nephropathy

The development of ESRD in patients with diabetes mellitus advances down a characteristic course depicted in Figure 1.[3] At the time that hyperglycemia is noted, the glomerular filtration rate is elevated due to increased renal plasma flow, renal hypertrophy, and augmented intraglomerular pressure. If the individual is susceptible to developing diabetic kidney disease, histologic changes characteristic of diabetic glomerulosclerosis begin to develop within 3 years. Microalbuminuria, the earliest clinical phase of diabetic kidney disease, develops approximately 7 to 10 years after clear histologic changes in the glomerular, tubulointerstitial, and vascular structures of the kidney are evident. Approximately 15 years after the onset of diabetes (ie, approximately 5 years after the onset of microalbuminuria) the glomerular filtration rate has returned to normal and overt proteinuria is present. The presence of overt proteinuria (>300 mg/dL of albumin or 500 mg/dL of total protein) is an ominous finding in a patient

Continued ☞

Figure 1. Natural Course of Diabetic Nephropathy

Time (yrs)	Test Results			Physiologic Status
	Glomerular Filtration Rate (ml/min)	Creatinine (mg/dL)	Blood Urea Nitrogen (mg/dL)	
-3	120	1.0	15	Normal
onset	150	0.8	10	Onset of Diabetes
3	150	0.8	10	Diabetic Glomerulosclerosis
15	120	1.0	15	Overt Proteinuria*
18	60	>2	>30	Overt Azotemia
20	<10	>10	>100	End Stage Renal Failure

*** Microalbuminuria generally occurs about 5 years before the onset of overt proteinuria**.

with diabetes mellitus since no intervention has been shown to prevent the ultimate progression to ESRD once this stage in the development of diabetic kidney disease has been reached.

Fortunately, aggressive metabolic interventions made at the onset of microalbuminuria will postpone and may prevent the development of ESRD in both Type 1 and Type 2 diabetic patients. Unfortunately, too few practitioners screen for microalbuminuria. Thus, in the majority of patients, diabetic nephropathy is not diagnosed until the disease has advanced to a point where it may be impossible to reverse. The detection of microalbuminuria and early intervention with ACE-inhibitor therapy are the focus of the remainder of this article.

...too few practitioners screen for microalbuminuria.

Microalbuminuria

Definition and Measurement. The mean value for the urinary albumin excretion rate (AER) in normal individuals is 10 mg/dL or 7 µg/min. Poor glucose control, urinary tract infections, heavy exercise, and contamination at the time of menstruation all may give abnormally high values. If the confounding conditions listed above are absent, most authorities consider an AER greater than 30 mg/dL or 20 µ/min to be clearly abnormal. An AER in excess of 300 mg/dL (or 500 mg of total protein) is defined as overt proteinuria.

A number of sampling methods have been employed to estimate urinary AER rates including timed collections (24-hour, overnight, 4-hour), and urine albumin to serum creatinine ratios obtained on spot collections. A dipstick (Micral®) sensitive enough to detect microalbuminuria was introduced by Boehringer Mannheim. The Micral® strip may be used as a sensitive, in-office screen if careful attention is given to the time of contact between the urine and test strip. When Micral® strips are used as a screening procedure, every positive Micral® test should be followed up with a complete 24-hour urine collection for determination of microalbuminuria and creatinine. The 24-hour urine AER is then used as the standard on which therapeutic decisions are based.

Treatment

Hypertension. Blood pressure control and specific treatment with ACE inhibitors is the most effective way to postpone and possibly prevent a further increase in urine protein excretion and deterioration of renal function.[4] The superior renal protective effects of the ACE-inhibitors may result from their ability to reduce intraglomerular pressure. Additionally, ACE-inhibition has been shown to block angiotensin II's direct growth-promoting effects on the kidney and to alter the charge selectivity of the glomerular

Continued ☞

basement membrane making it more difficult for the leakage of anionic proteins such as albumin. These nonhemodynamic effects of ACE-inhibitors may explain why there is a greater reduction in proteinuria with ACE-inhibitors compared with other classes of antihypertensive agents when comparable levels of blood pressure reduction are achieved.[5] It also may provide a rationale for using ACE-inhibitors to treat normotensive patients with microalbuminuria.

The ability of captopril to reduce the progression of microalbuminuria to overt proteinuria was tested in a multicenter, prospective, double-blind, placebo-controlled trial of 143 normotensive patients with IDDM.[6] At 2 years, 6% of the captopril-treated patients had progressed to overt proteinuria, compared with 18.6% of the placebo-treated subjects. Impressively, AER decreased at a rate of 17.9% per year in the captopril-treated group and increased by 11.8% per year in the placebo group over the study duration period. Enalapril was tested in a 5-year study involving 103 normotensive NIDDM patients.[7] Within 5 years, 7.7% (4/52) enalapril-treated subjects had developed proteinuria compared with 23.5% (12/51) of subjects given placebo. AER increased 12.3% per year in the placebo group but decreased 16.7% in the enalapril group.

Glycemic Control. The largest prospective study of the role of glycemic control in the prevention of diabetic complications, the Diabetes Control and Complications Trial (DCCT),[8] conclusively showed that intensive insulin therapy could delay the development of diabetic nephropathy. In this study of 1441 patients with IDDM, the intensively treated group (mean plasma glucose of 150 mg/dL) had a reduction in the incidence of the development of microalbuminuria of 39% and a 54% reduction in the development of overt albuminuria compared to the conventionally treated group (mean plasma glucose of 230 mg/dL).

Since the DCCT trial showed a continuous reduction of microvascular complications with improved glycemic control, it seems reasonable to attempt to achieve blood glucose levels as close to normal as possible in diabetics with microalbuminuria while avoiding significant hypoglycemia. In diabetics with established renal insufficiency, hypoglycemic reactions are more frequent and less stringent glucose control must often be accepted. The American Diabetes Association has recommended that intensive control in IDDM patients and NIDDM means a pre-meal blood glucose concentration of 80-120 mg/dL and 2 hr postprandial glucose levels of <180 mg/dL. This level of glycemic control corresponds to a HbA_{1c} of <7%.[9] A more realistic goal in diabetics with frequent hypoglycemia would be a HbA_{1c} of <8%, which corresponds to a premeal glucose level of 140 mg/dL and 2 hr postprandial values <200 mg/dL. The risk of developing microalbuminuria appears to increase abruptly at HbA_{1c} levels above 8.1.[10] Therefore, every effort should be made to maintain the blood glucose below 200 mg/dL in all diabetic patients.

The risk of developing microalbuminuria appears to increase abruptly at HbA_{1c} levels above 8.1.

Protein Restriction. It is well established that a diet high in protein increases intraglomerular pressure and leads to glomerular hypertrophy. Several studies have shown a significant reduction in albuminuria and a slowing in the rate of decline of the glomerular filtration rate when protein intake was reduced to 0.6 to 0.8 g/kg body weight per day.[11] This level of reduction is within the published ADA guidelines.[12] The effectiveness of low-protein diets in patients with renal failure was recently challenged by the results of a well-designed, prospective trial involving 840 patients with renal disease of various causes (3% of the study group had diabetes mellitus).[13] In this study, the decline in GFR was identical in the low protein intake group (0.58 g/kg/day) and the normal protein intake group (1.3 g/kg/day). It is likely that the concomitant use of the new antihypertensive medications in both groups mediated the beneficial effects of the low protein diet. In particular, almost half of the study patients were

Continued ☞

on ACE inhibitors, which have specific renal protective properties. Based on this study, it seems prudent to recommend modest protein restriction (0.9 - 1.0 g/kg/day) and aggressive blood pressure control in all patients with diabetic nephropathy.

Summary

The number of patients progressing to ESRD in the United State is increasing at an alarming rate. Near normalization of blood glucose represents primary prevention and should be the goal of therapy for all patients. The addition of ACE-inhibitor therapy to the treatment regimen at the earliest stage of diabetic nephropathy (microalbuminuria) offers the best hope that further deterioration in renal function can be delayed or prevented.

Prepared by Charles A. Reasner, MD, Associate Professor, Department of Medicine, Division of Endocrinology and Metabolism, University of Texas Health Science Center (UTHSC) at San Antonio; and Ralph A. DeFronzo, MD, Professor and Chief, Department of Medicine, Division of Diabetes, UTHSC at San Antonio.

References

1. Bloomgarden ZT. American Diabetes Association Scientific Sessions, 1995. Diabetes Care 1995;18:1402-1405.

2. Rostand SG, Kirk KA, Rutsky EA, Pate BA: Racial differences in the incidence of treatment for end-stage renal disease. N Engl J Med 1982;306:1276-1279.

3. DeFronzo RA. Diabetic nephropathy. Diabetes Rev (in press).

4. Kasiske BL, Kalil RSN, MA JZ, Liao M, Kean WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. Ann Intern Med 1993;118:129-138.

5. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456-1462.

6. Laffel LMB, McGill JB, Gans DJ. The beneficial effect of angiotension-converting-enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. Am J Med 1995;99:487-504.

7. Ahmad J, Siddiqui MA, Ahmad H. Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. Diabetes Care 1997;20:1576-1581.

8. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986.

9. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 1995;18 (Suppl 1): 8-15.

10. Krowlewski AS, Laffel LMB, Krowlewski M, Quinn M, Warram JH. Glycosolated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. N Engl J Med 1995;332:1251-1255.

11. Ponerlean J, Verdy M, Garrel DR, Nadean MH. Effect of protein intake on glycaemic control and renal function in type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1993;36:829-834.

12. Nutritional recommendations and principles for individuals with diabetes mellitus. Diabetes Care 1987;10:126-132.

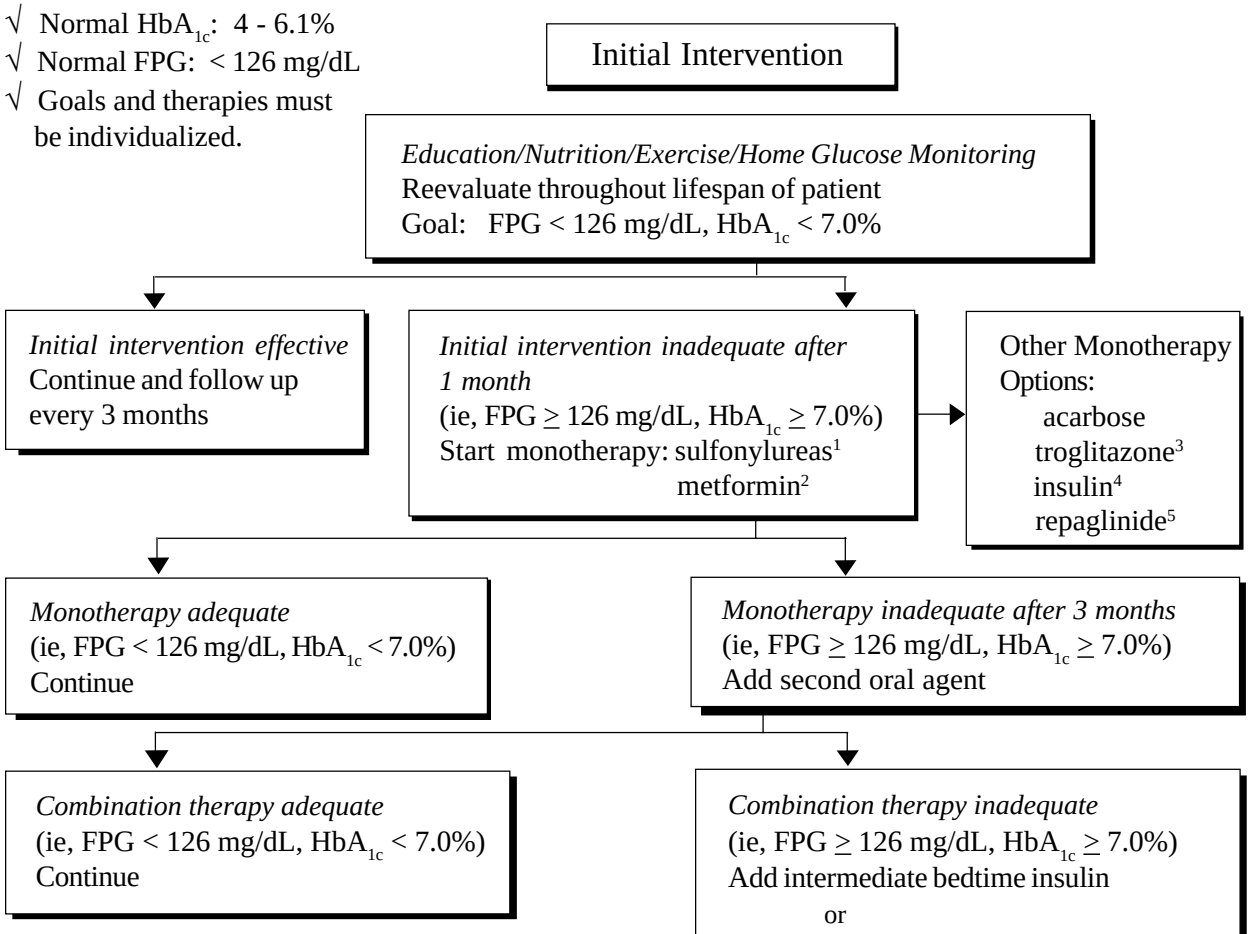
13. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. N Engl J Med 1994;330:877-884.

For further information contact Charles A. Reasner, MD, Associate Professor, Department of Medicine/Division of Endocrinology and Metabolism, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas, 78284-7877, Phone: (210) 358-3693, Fax: (210) 358-3289.

Management of Type 2 Diabetes

The Texas Diabetes Council Managed Care Work Group has recently updated its original *Pharmacological Algorithm for Type 2 Diabetes*. The proposed algorithm reflects new recommendations for what constitutes a normal fasting plasma glucose (NFPG < 126mg/dL) and incorporates new treatment options.

Pharmacological Algorithm for Type 2 Diabetes



[1] May cause hypoglycemia if FPG is only mildly elevated.

[2] Contraindicated in patients with impaired renal function (ie, serum creatinine >1.4 mg/dL in females and >1.5 mg/dL in males). Preferred if patient overweight or dyslipidemic.

[3] Should not be used in patients with abnormal liver functions (ie, > 1.5 times the upper limit of normal). When starting troglitazone, LFTs must be checked every month for the first 8 months, every other month for the next 4 months and periodically thereafter.

[4] If initial presentation with fasting glycemia is ≥ 260 mg/dL in a symptomatic patient, consider insulin as initial intervention.

[5] May rarely cause hypoglycemia if FPG is only mildly elevated.

Texas Diabetes Council
TEXAS DEPARTMENT OF HEALTH

Revised: 7/17/98

Legislation Affecting Persons With Diabetes

During the 1997 Texas Legislative Session, two bills were passed that affect insurance coverage for persons with diabetes.

Senate Bill 163 mandates that health benefit plans provide coverage for diabetes equipment, supplies, and self-management training programs to insured individuals diagnosed with diabetes. Among supplies that must be covered are blood glucose monitors and testing strips, syringes, prescriptive and nonprescriptive oral agents, insulin, visual reading strips, and urine test strips.

This bill mandates that training in diabetes management, including counseling in nutrition and in proper use of equipment and supplies, be provided by a health care practitioner who is licensed, registered, or certified. The Commissioner of Insurance is drafting rules for this new mandate.

Senate Bill 162 created the Texas Diabetes Care Pilot Program, which makes diabetes management services available to Medicaid recipients who have diabetes-related conditions and reside in selected areas of the state with high diabetes incidence and fatality rates. Criteria for site selection are also being developed. Also, the Texas Diabetes Council and Texas Department of Insurance will establish minimum standards for diabetes benefits provided through health benefit plans in Texas.

For updated information on either bill, contacts are provided below:

Senate Bill 163:

- For technical questions regarding insurance contracts, contact the Life/Health Group at (512) 322-3401.

- For technical questions regarding HMO contracts, contact the HMO Group at (512) 322-4266.

- For assistance with claims, contact the Texas Department of Insurance Consumer Help Line at (800) 252-3439.

- Watch for posting of draft rules as they become available on the Texas Department of Insurance web page: **www.tdi.state.tx.us**

Senate Bill 162:

Texas Diabetes Council/Texas Department of Health
(512) 458-7490

The American Diabetes Association, Texas Affiliate, Inc., has strongly supported passage of legislation that increases access to diabetes management services under health benefit plans available in Texas. Staff is interested in hearing about any problems or concerns associated with effective implementation of these bills, and may be reached at (800) 252-8233 x250.

In the News

Cryptosporidia: TDH Issues Final Brushy Creek Study Results

From July 21 through July 31, over 500 residents of Brushy Creek, a subdivision located between Round Rock and Austin, reported symptoms of gastrointestinal illness following a July 14 sewage spill at a City of Austin pump station. Texas Department of Health (TDH) laboratory tests confirmed the parasite *Cryptospiridium parvum* in 87 stool samples analyzed as of August 20.

From July 29 through July 31, TDH also conducted a survey of area residents to determine the scope of the outbreak. Results of the TDH investigation indicated that as many as 1,300 of the area's approximately 10,000 residents may have been infected with *C. parvum*. Although cryptoporidiosis is not usually life-threatening for healthy individuals, young children, the elderly, and persons with weakened immune systems could have complications from severe diarrhea or vomiting and should consult a physician if they experience these symptoms.

For further information contact David Bergmire-Sweat, TDH Infectious Disease Epidemiology and Surveillance Division, at (512) 458-7676.

Salmonella enteritidis Alert

Since July 1, 1998, the number of reports of *Salmonella enteritidis* cases statewide has increased by 45%. Reported cases are concentrated in the Northern and Eastern regions of Texas. One outbreak of *S. enteritidis* has been associated with the consumption of homemade ice cream made with raw eggs purchased in Hunt County. People are reminded to thoroughly cook eggs or use pasteurized eggs in their recipes to lower the risk of disease.

Symptoms of salmonellosis include diarrhea, headache, nausea, vomiting, fever, and abdominal pain. Health care providers are urged to consider a diagnosis of salmonellosis in patients presenting with these symptoms and who have a recent history of raw egg consumption.

Report any culture-confirmed cases of salmonellosis to your local health department by calling (800) 705-8868.

Disease Prevention News Reprints

Since publications of government agencies are public domain, DPN materials may be reproduced, without prior permission, using the following guidelines. Photocopied materials that include our masthead need no additional reference as to source. For portions reproduced exactly as published, please provide a full citation of *DPN* as the source. This guideline also applies to narrative that summarizes or rewords our material, keeping the same meaning. However, DPN material that is included in narrative containing material from other sources, especially when the text includes opinions not expressly stated as those of *DPN* or TDH, careful delineation among sources is essential. Use of materials reprinted in *DPN* from other sources requires permission from the original publisher.

For further reprint information contact Susan Hammack at (512) 458-7677.

Disease Prevention News (DPN)
Texas Department of health
1100 West 49th Street
Austin, Tx 78756-3199
Phone: 512-458-7677
Fax: 512-458-7616
Internet: dpn@discon.tdh.state.tx.us

The electronic versions of Disease Prevention News are available at the following locations:
http://www.tdh.state.tx.us/phpep/dpnhome/htam
TDH Health Texans BBS: (800) 858-5833

Get your *DPN* faster and easier !

Our new electronic mailing list services make snail mail, misrouted copies, and issues lost under a pile of paperwork a thing of the past! The advent of the Internet and electronic publishing has created an opportunity to disseminate important public health information much more quickly than is possible with traditional print methods. To take advantage of this technology, the Public Health Professional Education Program has created a new Disease Prevention (DPN) Electronic Mailing Service that provides two options.

Sign up for the *DPN* Notice Mailing List to receive email notices as soon as the most current electronic issue of DPN is available at the DPN Web Site. These biweekly notices will include the name and date of the issue, the file size of the electronic issue (in kilobytes), a table of contents, and a clickable link to the file. This option enables readers to download selected DPN issues from the World Wide Web of the Internet.

Readers who know they want to receive every issue of DPN can sign up for the DPN Issue Mailing List. In addition to the notice of the most recent DPN, these readers receive the actual DPN portable document format (pdf) file as an attachment to the email. The pdf files contain graphics and figures and are true representations of the printed version of DPN.

For further information and to sign up for these services, contact Linda Darlington at (512) 458-7677; ***email:*** **Linda.Darlington@tdh.state.tx.us**